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Addition of docetaxel, zoledronic acid, or both to first-line long-term hormone therapy in prostate cancer (STAMPEDE): survival results from an adaptive, multiarm, multistage, platform randomised controlled trial



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Summary

Background Long-term hormone therapy has been the standard of care for advanced prostate cancer since the 1940s. STAMPEDE is a randomised controlled trial using a multiarm, multistage platform design. It recruits men with high-risk, locally advanced, metastatic or recurrent prostate cancer who are starting first-line long-term hormone therapy. We report primary survival results for three research comparisons testing the addition of zoledronic acid, docetaxel, or their combination to standard of care versus standard of care alone.

Methods Standard of care was hormone therapy for at least 2 years; radiotherapy was encouraged for men with N0M0 disease to November, 2011, then mandated; radiotherapy was optional for men with node-positive non-metastatic (N+M0) disease. Stratified randomisation (via minimisation) allocated men 2:1:1:1 to standard of care only (SOC-only; control), standard of care plus zoledronic acid (SOC+ZA), standard of care plus docetaxel (SOC+Doc), or standard of care with both zoledronic acid and docetaxel (SOC+ZA+Doc). Zoledronic acid (4 mg) was given for six 3-weekly cycles, then 4-weekly until 2 years, and docetaxel (75 mg/m²) for six 3-weekly cycles with prednisolone 10 mg daily. There was no blinding to treatment allocation. The primary outcome measure was overall survival. Pairwise comparisons of research versus control had 90% power at 2.5% one-sided α for hazard ratio (HR) 0.75, requiring roughly 400 control arm deaths. Statistical analyses were undertaken with standard log-rank-type methods for time-to-event data, with hazard ratios (HRs) and 95% CIs derived from adjusted Cox models. This trial is registered at ClinicalTrials.gov (NCT00268476) and ControlledTrials.com (ISRCTN78818544).

Findings 2962 men were randomly assigned to four groups between Oct 5, 2005, and March 31, 2013. Median age was 65 years (IQR 60–71). 1817 (61%) men had M+ disease, 448 (15%) had N+/X M0, and 697 (24%) had N0M0. 165 (6%) men were previously treated with local therapy, and median prostate-specific antigen was 65 ng/mL (IQR 23–184). Median follow-up was 43 months (IQR 30–60). There were 415 deaths in the control group (347 [84%] prostate cancer). Median overall survival was 71 months (IQR 32 to not reached) for SOC-only, not reached (32 to not reached) for SOC+ZA (HR 0.94, 95% CI 0.79–1.11; $p=0.450$), 81 months (41 to not reached) for SOC+Doc (0.78, 0.66–0.93; $p=0.006$), and 76 months (39 to not reached) for SOC+ZA+Doc (0.82, 0.69–0.97; $p=0.022$). There was no evidence of heterogeneity in treatment effect (for any of the treatments) across prespecified subsets. Grade 3–5 adverse events were reported for 399 (32%) patients receiving SOC, 197 (32%) receiving SOC+ZA, 288 (52%) receiving SOC+Doc, and 269 (52%) receiving SOC+ZA+Doc.

Interpretation Zoledronic acid showed no evidence of survival improvement and should not be part of standard of care for this population. Docetaxel chemotherapy, given at the time of long-term hormone therapy initiation, showed evidence of improved survival accompanied by an increase in adverse events. Docetaxel treatment should become part of standard of care for adequately fit men commencing long-term hormone therapy.

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Research in context

Evidence before this study

Systemic treatment has changed little for newly diagnosed men with high-risk locally advanced or metastatic prostate cancer since the development of gonadotropin-releasing hormone analogues a generation ago. The only major change has been the use of radical radiotherapy for men whose disease had not spread. This century, new agents began to show valuable activity in relapsed, metastatic, castrate-refractory prostate cancer—including zoledronic acid, which was approved in 2002 on the basis of reduced morbidity in men with bone metastases (a site of spread in up to 90% of castrate-refractory prostate cancer), and docetaxel, with improved survival demonstrated in 2004. Several other trials in addition to STAMPEDE have assessed both drugs in the newly diagnosed setting, most notably GETUG-15 and CHAARTED, which assessed docetaxel in the metastatic setting (about 60% of the population used in our trial). A systematic review and meta-analysis was done in parallel to preparation of this report and contains details of the review strategy.

Added value of this study

Our results for zoledronic acid show no convincing evidence of worthwhile benefit either on failure-free or overall survival.

Introduction

Since October, 2005, the STAMPEDE randomised controlled trial has recruited men with metastatic (M1), high-risk localised (N0), or node-positive (N+) prostate cancer who were newly diagnosed or had high-risk recurrent disease following previous local therapy. All were commencing first-line long-term hormone therapy. Prognosis for these patient groups had altered little since the first description of the effects of hormone therapy in the 1940s. This began to change in the early 21st century with licensing of agents that improved survival (ie, docetaxel, abiraterone, enzalutamide, cabazitaxel, radium-223, and sipuleucel-T),¹⁻⁸ and disease-modifying agents that reduced morbidity (zoledronic acid and denosumab).^{9,10} However, these agents have all shown their benefits in the setting of castrate-refractory prostate cancer (ie, after first-line hormone therapy has ceased working).

STAMPEDE uses a multiarm, multistage (MAMS) platform design to test whether the addition of treatments at the time of long-term hormone therapy initiation improves overall survival. Here, we evaluate and report findings for zoledronic acid and docetaxel; data for celecoxib, abiraterone, enzalutamide in combination with abiraterone, and (in patients with newly diagnosed metastatic disease only) prostate radiotherapy will be reported elsewhere. We have previously reported the celecoxib-containing groups which closed to recruitment early after a pre-planned second intermediate analysis failed to show sufficient effect on failure-free survival.¹¹ We have also previously

These results are congruent with emerging results from other trials in men starting long-term hormone therapy. The docetaxel results showed an improvement in overall survival (HR 0.78; 95% CI 0.66–0.93; $p=0.006$). There was a notable improvement in survival for the metastatic subset, which is consistent with findings from GETUG-15 and CHAARTED which both also showed gains in failure-free survival with docetaxel. GETUG-15 showed a non-significant improvement in overall survival, and CHAARTED reported a statistically significant improvement in overall survival.

Implications of all the available evidence

Together, these trials provide evidence that six cycles of docetaxel should be added to standard androgen deprivation therapy for men with metastatic disease commencing treatment. Men with non-metastatic disease had better prognoses, and failure-free survival was clearly improved by docetaxel; however, there were relatively few deaths in those with non-metastatic disease, so statements about overall survival in this population remain underpowered.

reported control group outcome data for patients with metastatic¹² and non-metastatic¹³ disease. We report here the first survival data for the following original groups in this platform trial: zoledronic acid, docetaxel, and their combination. Other trials have also examined similar strategies, both in patients with non-metastatic disease and in those with metastatic disease, usually with single drugs. A meta-analysis with other docetaxel and zoledronic acid-containing trials has been conducted and is reported separately.¹⁴

Zoledronic acid was licensed in 2002 on the basis of an improvement in a composite outcome measure of time to first skeletal-related event, with a risk ratio of 0.64 (95% CI 0.49 to 0.85) in castrate-refractory prostate cancer, and subsequent reduction in further skeletal-related events using the 4 mg schedule.⁹ There was limited evidence of a benefit in survival, although the study was underpowered. Two previous UK trials, PR04 and PR05, used sodium clodronate in patients with non-metastatic and metastatic disease, respectively. The PR05 trial showed improved survival with concurrent hormone therapy plus clodronate but no evidence of benefit was seen in PR04.¹⁵

Docetaxel (75 mg/m²) 3-weekly (ie, given every 3 weeks) was licensed for metastatic castrate-refractory prostate cancer in 2004, on the basis of two trials comparing mitoxantrone and prednisone with docetaxel and either prednisone² or estramustine.¹ The median survival benefit observed was about 3 months, with a hazard ratio (HR) of 0.76 (0.62–0.94)² for docetaxel compared with mitoxantrone.

The STAMPEDE trial^{16,17} used interim activity analyses, based on failure-free survival, to select groups to continue accrual for fully powered survival analysis. We report here overall, failure-free, and prostate-cancer-specific survival data from the zoledronic acid and docetaxel groups and their combination, together with adverse event data and treatment after relapse.

Methods

Study design and participants

We used a MAMS platform trial approach, incorporating a seamless phase 2/3 design.¹⁸ The rationale and design have been described previously.^{16,17,19} Full details are in the protocol. In summary, eligible patients had prostate cancer that was newly diagnosed as metastatic, node positive, or high-risk locally advanced (with at least two of T3/4, Gleason score of 8–10, and prostate-specific antigen ≥ 40 ng/mL); or previously treated with radical surgery, radiotherapy, or both and relapsing with high-risk features. All patients were intended for long-term hormone therapy, started no longer than 12 weeks before randomisation. There were no age restrictions; patients were required to be fit for chemotherapy with no clinically significant cardiovascular history.

Randomisation and masking

Patients were randomised centrally using a computerised algorithm, developed and maintained by the trials unit. Minimisation with a random element of 80% was used, stratifying for hospital, age at randomisation, presence of metastases, planned radiotherapy use, nodal involvement, WHO performance status, planned hormone therapy, and regular use of aspirin or another non-steroidal anti-inflammatory drug. Allocation was in a 2:1:1:1 ratio to standard of care only (SOC-only), standard of care plus zoledronic acid (SOC+ZA), standard of care plus docetaxel (SOC+Doc), or standard of care plus zoledronic acid and docetaxel (SOC+ZA+Doc). Masking to treatment allocation was considered impracticable and of limited value given the primary outcome measure.

Procedures

Standard of care was hormone therapy for at least 2 years with gonadotropin-releasing hormone agonists or antagonists or, only between 2006 and 2011 for patients with non-metastatic disease, oral anti-androgens alone. Orchidectomy was an allowable alternative to drug therapy. No recommendations around the use of granulocyte colony stimulating factor with docetaxel were given. Radiotherapy, at 6–9 months after randomisation, was

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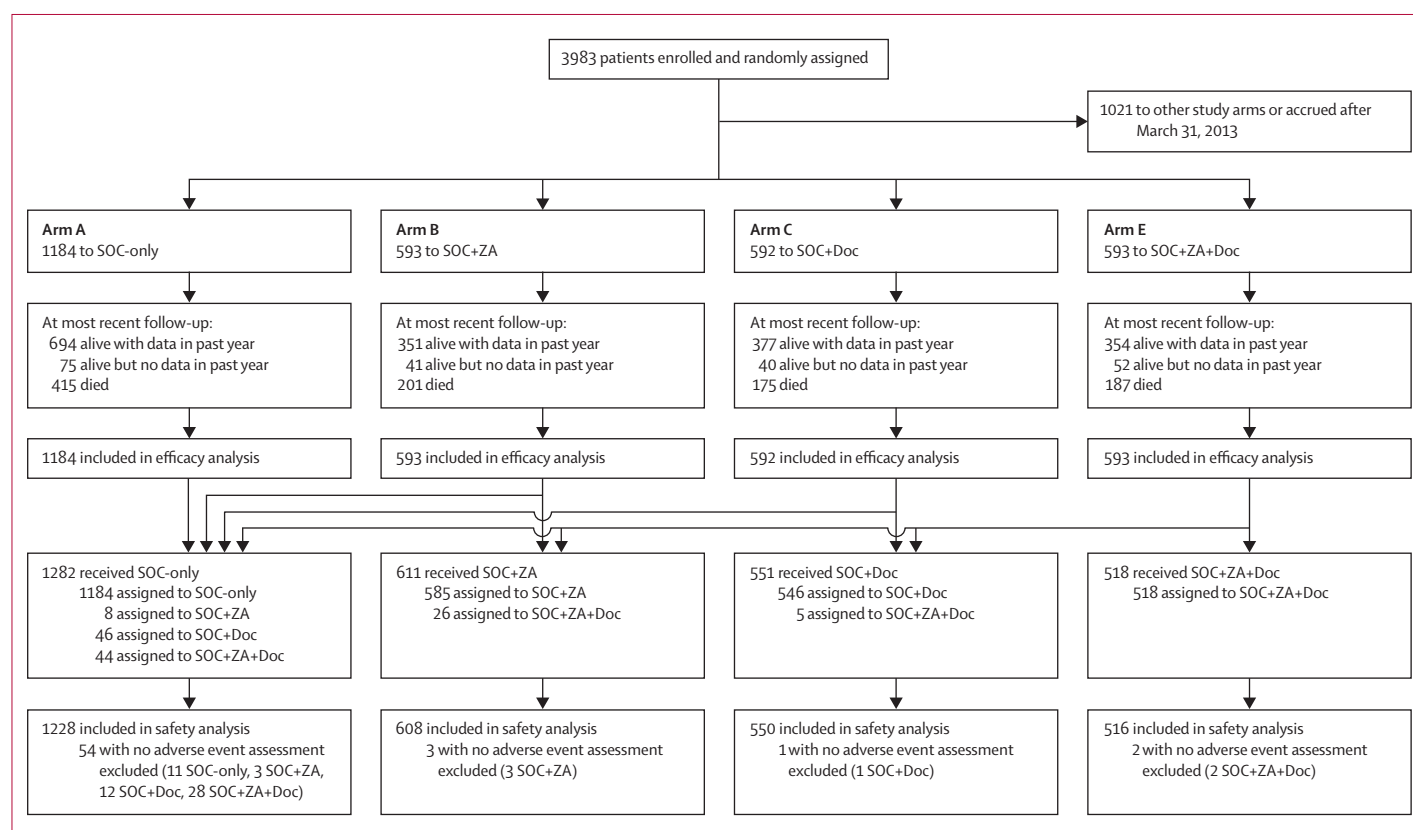


Figure 1: Trial profile

SOC-only=standard of care only. SOC + ZA=standard of care plus zoledronic acid. SOC + Doc=standard of care plus docetaxel. SOC + ZA + Doc=standard of care plus zoledronic acid and docetaxel.

	Standard of care (n=1184)	Standard of care plus zoledronic acid (n=593)	Standard of care plus docetaxel (n=592)	Standard of care plus zoledronic acid and docetaxel (n=593)
Age, years				
Median (IQR)	65 (60–70)	66 (61–71)	65 (61–71)	66 (60–70)
Range	41–82	42–82	40–81	42–84
Prostate-specific antigen (ng/mL)				
Median (IQR)	67 (23–200)	59 (22–172)	70 (27–181)	63 (21–183)
Range	0–15747	0–13300	1–9999	1–8503
Days from diagnosis				
Median (IQR)	75 (55–99)	76 (56–101)	76 (56–99)	76 (56–100)
Range	0–4070	1–4174	3–5033	6–4485
Missing	5	8	7	6
Pain from prostate cancer				
Absent	984 (85%)	496 (84%)	490 (84%)	483 (84%)
Present	179 (15%)	93 (16%)	96 (16%)	94 (16%)
Missing	21	4	6	16
T category at randomisation				
T0	7 (1%)	3 (1%)	2 (0%)	2 (0%)
T1	21 (2%)	7 (1%)	0 (0%)	5 (1%)
T2	113 (10%)	53 (9%)	60 (10%)	67 (11%)
T3	756 (64%)	395 (67%)	390 (66%)	371 (63%)
T4	211 (18%)	92 (16%)	105 (18%)	100 (17%)
TX	76 (6%)	43 (7%)	35 (6%)	48 (8%)
N category at randomisation				
N0	522 (44%)	258 (44%)	260 (44%)	265 (45%)
N+	594 (50%)	303 (51%)	298 (50%)	293 (49%)
NX	68 (6%)	32 (5%)	34 (6%)	35 (6%)
Metastases				
None	460 (39%)	227 (38%)	230 (39%)	228 (38%)
Any metastases	724 (61%)	366 (62%)	362 (61%)	365 (62%)
Bone metastases	634 (54%)	302 (51%)	307 (52%)	310 (52%)
Liver metastases	15 (1%)	12 (2%)	6 (1%)	9 (2%)
Lung metastases	33 (3%)	17 (3%)	13 (2%)	14 (2%)
Nodal metastases	220 (19%)	120 (20%)	102 (17%)	116 (20%)
Other metastases	46 (4%)	33 (6%)	25 (4%)	21 (4%)
Broad disease grouping				
Newly diagnosed N0M0	256 (22%)	120 (20%)	131 (22%)	131 (22%)
Newly diagnosed N+M0	171 (14%)	88 (15%)	86 (15%)	76 (13%)
Newly diagnosed M1	690 (58%)	351 (59%)	347 (59%)	350 (59%)
Previously treated M0	33 (3%)	19 (3%)	13 (2%)	21 (4%)
Previously treated M1	34 (3%)	15 (3%)	15 (3%)	15 (3%)
Gleason sum score				
≤7	282 (24%)	122 (21%)	110 (19%)	117 (20%)
8–10	810 (68%)	421 (71%)	436 (74%)	425 (72%)
Unknown	92 (8%)	50 (8%)	46 (8%)	51 (9%)
Aspirin or NSAID use				
No	891 (75%)	448 (76%)	444 (75%)	445 (75%)
Yes	293 (25%)	145 (24%)	148 (25%)	148 (25%)
Planned or current hormone therapy*				
Orchiectomy	5 (0%)	4 (1%)	2 (0%)	3 (1%)
LHRH-based	1166 (98%)	581 (98%)	581 (98%)	582 (98%)
Bicalutamide	11 (1%)	7 (1%)	9 (2%)	8 (2%)

(Table 1 continues on next page)

encouraged for patients with N0M0 disease, until November, 2011, then mandated; radiotherapy was optional for patients with N+M0 disease; staging was with the Union for International Cancer Control (UICC) TNM staging criteria. Guidance on radiotherapy techniques are described elsewhere.¹³ Zoledronic acid (4 mg) was given for six 3-weekly cycles, then 4-weekly until 2 years. Docetaxel (75 mg/m²) was given for six 3-weekly cycles with prednisolone (10 mg) daily, and standard premedication before each injection. Dose modifications were described in the protocol. Trial therapy was discontinued after disease progression or intolerable adverse events.

Patients were followed up 6-weekly to 6 months, 12-weekly to 2 years, 6-monthly to 5 years, then annually. Prostate-specific antigen was measured at every follow-up; further tests were at the clinician's discretion. Nadir prostate-specific antigen was the lowest value reported within 24 weeks after enrolment. Adverse events were graded with Common Toxicity Criteria (CTCAE) version 3.0; toxic effects and symptoms were reported at regular follow-up visits. Serious adverse events, including serious adverse reactions, were reported accordingly. The trial was done in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki, and had the relevant regulatory and ethics approvals (eg, in the UK we obtained national ethics approval, national regulatory approval, and local implementation). All patients gave written, informed consent.

Outcomes

The definitive and intermediate primary outcome measures were overall survival and failure-free survival, respectively. Overall survival was defined as time from randomisation to death from any cause. Failure-free survival, which is commonly used to drive decisions in the clinic, was selected because it is on the causal pathway to death from prostate cancer and was not required to be a surrogate for overall survival. It was defined as time from randomisation to first evidence of at least one of: biochemical failure; progression either locally, in lymph nodes, or in distant metastases; or death from prostate cancer. Biochemical failure was defined as a rise of 50% above the within-24-week nadir and above 4 ng/mL and confirmed by retest or treatment.¹² We expected prostate-specific antigen failure to be the most common manifestation of failure-free survival events. Cause of death was determined by masked central review. Death from prostate cancer was recorded when classified by the reviewer as “definitely” or “probably” prostate cancer. The site investigator's determination was used for deaths not yet reviewed.

Statistical analysis

The sample size was calculated using nstage and its predecessor programmes in Stata, which enables design of MAMS trials.²⁰ Assuming, for the control group, 2 years' median failure-free survival, and median overall survival between 4 and 5 years, we targeted a 25% relative

improvement (HR 0·75) in both failure-free survival and overall survival for each comparison of research group with control. Accumulating data were reviewed by an Independent Data Monitoring Committee, guided by lack-of-benefit stopping guidelines.^{16–18} The efficacy stage analysis of each pairwise comparison of research against control for overall survival required around 400 deaths in the control arm for 90% power and 2·5% one-sided α (corresponding to a two-sided α of 5%), accounting for three intermediate analyses on failure-free survival (analysed March, 2010, April, 2011, and May, 2012). The research groups within STAMPEDE were seen to test distinct hypotheses, and the trial was purposely not designed as a factorial trial.¹⁷ In this situation, many methodologists would not be concerned about the family-wise error rate.^{3,21–23} However, for completeness we calculated the maximum family-wise error rate as 6·75% for these three research groups.

Patients without the event of interest were censored at the time last known to be event free. Standard survival analysis methods were used to analyse time-to-event data. Cox proportional hazards regression models were used to estimate most relative treatment effects. This model was adjusted for stratification factors (except hospital and planned hormone therapy), and stratified by time periods defined by addition of a new research group or end in recruitment to an ongoing research group. An HR below 1·00 favoured the research group. Flexible parametric models were constructed with 4 degrees of freedom for each of the baseline hazard function and time-dependent effect, and adjusted for stratification factors and time periods.²⁴ Medians and 5-year estimates come from the flexible parametric model fitted to the data; these are more reliable than reading the Kaplan-Meier curves. The proportional hazards assumption was tested; restricted mean survival time was emphasised in the presence of non-proportionality. Fine and Gray regression models were used for competing risk analysis of prostate-cancer-specific survival (non-metastatic prostate-cancer-specific survival analyses did not adjust for time period due to lack of convergence). Prespecified analyses looked at consistency of treatment effect within stratification factors, over time period, and also by categorised Gleason score (≤ 7 , 8+, unknown), recurrent disease, and prostate-specific antigen values before hormone therapy. The statistical analysis plan was modified to include an analysis of the subset of patients with metastatic disease at randomisation after the presentation of CHAARTED²⁵ and GETUG-15²⁶ and before this primary analysis was performed. All tests were two-sided, with confidence intervals given at the 95% level.

Median follow-up was determined through the standard approach of reverse-censoring on death, in which survival is treated as the event and death as censoring. All patients are included in the efficacy analyses according to allocated treatment on an intention-to-treat basis. Adverse event data are shown for the safety population, comprising

	Standard of care (n=1184)	Standard of care plus zoledronic acid (n=593)	Standard of care plus docetaxel (n=592)	Standard of care plus zoledronic acid and docetaxel (n=593)
(Continued from previous page)				
Maximum androgen blockade	2 (0%)	1 (0%)	0 (0%)	0 (0%)
Time to starting hormone therapy (days)				
Median (IQR)	-41 (-63 to -20)	-40 (-62 to -20)	-43 (-66 to -21)	-43 (-63 to -22)
Range	-105 to 77	-193 to 32	-108 to 45	-142 to 28
Missing	1	0	2	0
Planned anti-androgen use				
No	102 (9%)	67 (12%)	52 (9%)	57 (10%)
Short-term anti-androgen	876 (76%)	420 (72%)	437 (75%)	434 (75%)
Long-term anti-androgen	178 (15%)	95 (16%)	92 (16%)	91 (16%)
Missing	28	11	11	11
Radiotherapy planned				
No	844 (71%)	421 (71%)	424 (72%)	423 (71%)
Yes	340 (29%)	172 (29%)	168 (28%)	170 (29%)
Does patient smoke?				
No	1006 (87%)	492 (84%)	506 (86%)	496 (84%)
Yes	157 (13%)	93 (16%)	81 (14%)	92 (16%)
Missing on assessment	16	6	4	4
Assessment not received	5	2	1	1
Does patient have diabetes				
No	1058 (90%)	544 (92%)	535 (91%)	516 (88%)
Yes, type 1	29 (2%)	11 (2%)	26 (4%)	16 (3%)
Yes, type 2	89 (8%)	36 (6%)	30 (5%)	57 (10%)
Missing on assessment	3	0	0	3
Assessment not received	5	2	1	1
Myocardial infarction				
No	1146 (97%)	578 (98%)	575 (98%)	571 (97%)
Yes, but still fit for trial	31 (3%)	13 (2%)	14 (2%)	18 (3%)
Missing on assessment	2	0	2	3
Assessment not received	5	2	1	1
Cerebrovascular disease				
No	1164 (99%)	579 (98%)	583 (99%)	580 (98%)
Yes, but still fit for trial	13 (1%)	12 (2%)	6 (1%)	9 (2%)
Missing on assessment	2	0	2	3
Assessment not received	5	2	1	1
Congestive heart failure				
No	1172 (100%)	588 (99%)	588 (100%)	589 (100%)
Yes, but still fit for trial	5 (0%)	3 (1%)	2 (0%)	0 (0%)
Missing on assessment	2	0	1	3
Assessment not received	5	2	1	1

(Table 1 continues on next page)

patients who received any study drug and underwent adverse event assessment, and analysed according to treatment initiated irrespective of study group assignment; a sensitivity analysis of safety was done on an intention-to-treat basis. Safety data were assessed continuously; we also present a safety analysis at 1 year, chosen to assess whether chemotherapy side-effects had ameliorated by this timepoint. A formal comparison of those research groups showing a survival advantage, compared with SOC-only,

For the **STAMPEDE trial protocol** see <http://www.stampede-trial.org>

For the **Common Toxicity Criteria** see http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcae-v3.pdf

	Standard of care (n=1184)	Standard of care plus zoledronic acid (n=593)	Standard of care plus docetaxel (n=592)	Standard of care plus zoledronic acid and docetaxel (n=593)
(Continued from previous page)				
Angina				
No	1138 (97%)	567 (96%)	574 (97%)	569 (97%)
Yes, but still fit for trial	39 (3%)	24 (4%)	17 (3%)	20 (3%)
Missing on assessment	2	0	0	3
Assessment not received	5	2	1	1
Hypertension				
No	741 (63%)	384 (65%)	383 (65%)	385 (65%)
Yes, but still fit for trial	437 (37%)	206 (35%)	208 (35%)	204 (35%)
Missing on assessment	1	1	0	3
Assessment not received	5	2	1	1

Data are median (IQR), range, or n (%). NSAID=non-steroidal anti-inflammatory drug. LHRH=luteinising hormone-releasing hormone. *Further information provided in the appendix.

Table 1: Baseline characteristics

	Standard of care plus zoledronic acid (n=593)	Standard of care plus zoledronic acid and docetaxel (n=593)
Numbers reporting starting	585 (99%)	544 (92%)
Numbers not reporting starting	8 (1%)	49 (8%)
Time to starting from randomisation, weeks	1.9 (1.0–2.9)	2.4 (1.6–3.7)
Time from starting hormone therapy to starting zoledronic acid, weeks	8.0 (5.0–11.3)	8.6 (5.9–11.9)
Time from starting to last administration, months	16.6 (7.8–23.2)	19.5 (9.1–23.4)
Reported reasons for stopping (if started):		
Treatment complete	206 (35%)	218 (40%)
Progressive disease	231 (39%)	119 (22%)
Toxicity	43 (7%)	66 (12%)
Unknown	38 (6%)	41 (8%)
Treatment refusal*	26 (4%)	46 (8%)
Dental treatment	11 (2%)	23 (4%)
Death	15 (3%)	13 (2%)
Intercurrent illness	5 (1%)	12 (2%)
Other	10 (2%)	6 (1%)

*Including treatment refusal, patient decision, clinician decision, administrative reasons, and withdrawal from trial.

Table 2: Treatment with zoledronic acid

See [Online](#) for appendix

was done, and a pre-planned factorial analysis (without an interaction term) is included for completeness. Data on first skeletal-related event and osteonecrosis of the jaw are also presented. All other analyses are exploratory. Statistical analyses were done with Stata version 14 and nstage. The trial is registered at ClinicalTrials.gov (NCT00268476) and ControlledTrials.com (ISRCTN78818544).

Role of the funding source

The trial was sponsored by the MRC and conducted by the MRC Clinical Trials Unit at UCL with the Swiss Group for Clinical Cancer Research. MRC employees were central to the conduct of the trial and the development of this

manuscript. Only authors MRSp and MRSy had access to raw data; processed data released by the Independent Data Monitoring Committee and Trial Steering Committee were available to all coauthors. Cancer Research UK (MRC PR08, CRUK/06/019) approved, but had no further input into, the trial design. Pfizer, Novartis, and Sanofi-Aventis approved the initial and amended trial design and participated in discussions on the progress of the trial. Representatives from these industry partners were invited to comment on the report. The analyses were driven by prespecified criteria and the decision to submit for publication was made by the Trial Management Group.

Results

Between Oct 5, 2005, and March 31, 2013, 2962 patients were randomised from more than 100 UK and Swiss sites: 1184 to SOC-only, 593 SOC+ZA, 592 SOC+Doc, and 593 SOC+ZA+Doc. Data were frozen on May 13, 2015, with a cutoff of March 4, 2015. The appendix shows an overview of the broader trial design and groups recruiting over time, whereas figure 1 shows the CONSORT flow diagram for analyses presented here. Table 1 gives baseline characteristics of these patients. Median follow-up was 43 months (IQR 30–60). Most patients (94%) were newly diagnosed. 1738 (62%) of 2797 newly diagnosed patients had metastatic disease at entry, compared with 79 (48%) of 165 patients with recurrent disease. Median age was 65 years (IQR 60–71), median prostate-specific antigen 65 ng/mL (IQR 23–184), and 2092 (71%) patients were Gleason score 8–10.

Median time to starting zoledronic acid was about 2 weeks after randomisation, and about 8 weeks from starting hormone therapy (most patients started hormone therapy before randomisation). Median duration of zoledronic acid was 16.6 months (IQR 7.8–23.2) for SOC+ZA and 19.5 months (IQR 9.1–23.4) for SOC+ZA+Doc, with the difference in duration being driven by differences in time to progression (table 2). Of patients allocated to receive zoledronic acid as part of trial treatment, overall about 40% of patients completed 2 years of zoledronic acid therapy (table 2). When less than 2 years of treatment was received, progression was the most common reason for stopping. Zoledronic acid was not started in eight (1%) patients assigned to SOC+ZA and 49 (8%) patients assigned to SOC+ZA+Doc, mostly due to treatment refusal.

Median time to starting docetaxel was about 2 weeks after randomisation and 9 weeks after starting hormone therapy. Of patients allocated to receive docetaxel as part of trial treatment, 456 (77%) patients assigned to SOC+Doc and 422 (71%) to SOC+ZA+Doc received the full six cycles, whereas 477 (81%) assigned to SOC+Doc and 446 (75%) to SOC+ZA+Doc received at least five cycles (table 3). When five or fewer cycles were reported, toxic effects were the most common reason for stopping (table 3), with few patients reporting stopping for disease progression. Docetaxel was not started in 46 (8%) patients

assigned to SOC+Doc and 70 (12%) to SOC+ZA+Doc, again mostly due to treatment refusal, patient choice, or withdrawal from the trial.

Planned use of standard of care radiotherapy was similar across groups (28–29%), with reported use being 323 (27%) patients for SOC-only; 155 (26%) for SOC+ZA; 154 (26%) for SOC+Doc; and 148 (25%) for SOC+ZA+Doc. In patients with non-metastatic disease, 62% were planned for radiotherapy, with the corresponding figures for reported use being 289 (63%) for SOC-only, 136 (60%) for SOC+ZA, 131 (57%) for SOC+Doc, and 130 (57%) for SOC+ZA+Doc; higher proportions of N0 than N+ patients received radiotherapy (appendix page 9).

There were 415 deaths (347 prostate cancer deaths; 84%) in patients receiving SOC-only; median survival was 71 months (IQR 32 to not reached) and 5-year survival was 55%. These data form the reference for each comparison of research group with control.

201 patients in the SOC+ZA group died (169 prostate cancer; 84%), with no evidence of a survival advantage compared with SOC-only (HR 0.94, 95% CI 0.79–1.11; $p=0.450$); median survival was not reached (IQR 32 to not reached), and 5-year survival was 57%. However, there was evidence of a survival advantage for SOC+Doc (HR 0.78, 95% CI 0.66–0.93; $p=0.006$) with 175 deaths (143 prostate cancer; 82%), median survival 81 months (IQR 41 to not reached), and 5-year survival of 63%. There was also evidence of survival advantage for SOC+ZA+Doc (HR 0.82, 95% CI 0.69–0.97; $p=0.022$) with 187 deaths (150 prostate cancer; 80%), median survival 76 months (IQR 39 to not reached), and 5-year survival of 60%. There was no evidence of non-proportional hazards. Plots for survival are shown in figure 2.

We found no evidence of heterogeneity of treatment effect across predefined subsets (figure 3). Pre-planned subset analyses in all 1817 patients with metastatic disease at randomisation included around 500 deaths per comparison. This included 350 deaths in patients on SOC-only (median survival 45 months [IQR 23–91], 5-year survival 39%). There were 170 deaths on SOC+ZA (HR 0.93, 95% CI 0.77–1.11; $p=0.416$), with median survival 46 months (IQR 24 to not reached) and 5-year survival of 43%. There were 144 deaths on SOC+Doc (HR 0.76, 95% CI 0.62–0.92; $p=0.005$), with median survival 60 months (IQR 27–103) and 5-year survival of 50% (appendix page 5). Finally, there were 158 deaths on SOC+ZA+Doc (HR 0.79, 95% CI 0.66–0.96; $p=0.015$), with median survival 55 months (IQR 29–88) and 5-year survival of 46%. Similar comparisons in patients without metastatic disease at randomisation are immature at this time, with fewer than 100 deaths per comparison.

Comparing the two research groups that demonstrated a survival advantage over the control group (SOC+Doc and SOC+ZA+Doc), we noted no evidence of an advantage when adding zoledronic acid to docetaxel (HR 1.06, 95% CI

	Standard of care plus docetaxel (n=592)	Standard of care plus zoledronic acid and docetaxel (n=593)
Numbers reporting starting	546 (92%)	523 (88%)
Numbers not reporting starting	46 (8%)	70 (12%)
Time to starting from randomisation, weeks	2.1 (1.6–3.1)	2.4 (1.6–3.7)
Time from starting hormone therapy to starting docetaxel, weeks	8.6 (5.6–11.9)	8.7 (5.9–11.7)
Number of cycles reported:		
0	46 (8%)	70 (12%)
1	27 (5%)	22 (4%)
2	17 (3%)	19 (3%)
3	12 (2%)	18 (3%)
4	13 (2%)	18 (3%)
5	21 (4%)	24 (4%)
6	456 (77%)	422 (71%)
Reported reasons for stopping (if started):		
Treatment complete	454 (83%)	423 (81%)
Toxicity	72 (13%)	66 (13%)
Treatment refusal*	6 (1%)	8 (2%)
Progressive disease	5 (1%)	8 (2%)
Intercurrent illness	5 (1%)	7 (1%)
Death	2 (0%)	5 (1%)
Unknown	2 (0%)	5 (1%)
Dental treatment	0 (0%)	1 (0%)

*Including treatment refusal, patient decision, clinician decision, and withdrawal from trial. Not all patients who reported stopping reason as "treatment complete" reported six cycles; similarly, not all patients reporting six cycles reported stopping reason as "treatment complete".

Table 3: Treatment with docetaxel

0.86–1.30; $p=0.592$). In an exploratory analysis of the effect of docetaxel on survival in the context of zoledronic acid (ie, comparing SOC+ZA with SOC+ZA+Doc), the hazard ratio was 0.87 (95% CI 0.71–1.06). Analysis of the main effects of zoledronic acid and docetaxel in a single factorial model, without a treatment-interaction term, showed docetaxel to be associated with a survival advantage (HR 0.82, 95% CI 0.72–0.93; $p=0.003$), but not zoledronic acid (HR 0.98, 95% CI 0.86–1.11; $p=0.726$). An exploratory factorial model, including an interaction term, found no evidence of treatment interaction ($p=0.401$); the individual treatment effects were the same as in the pairwise comparisons.

Figure 2 shows the failure-free survival plot for each research comparison, and the appendix page 10 shows the form of that failure-free survival event. There were 761 events in patients on SOC-only; median failure-free survival 20 months; 5-year failure-free survival 28%. With 374 events there was no evidence of improvement in failure-free survival with SOC+ZA (HR 0.92, 95% CI 0.81–1.04; $p=0.198$); median failure-free survival was 22 months and 5-year failure-free survival was 31%.

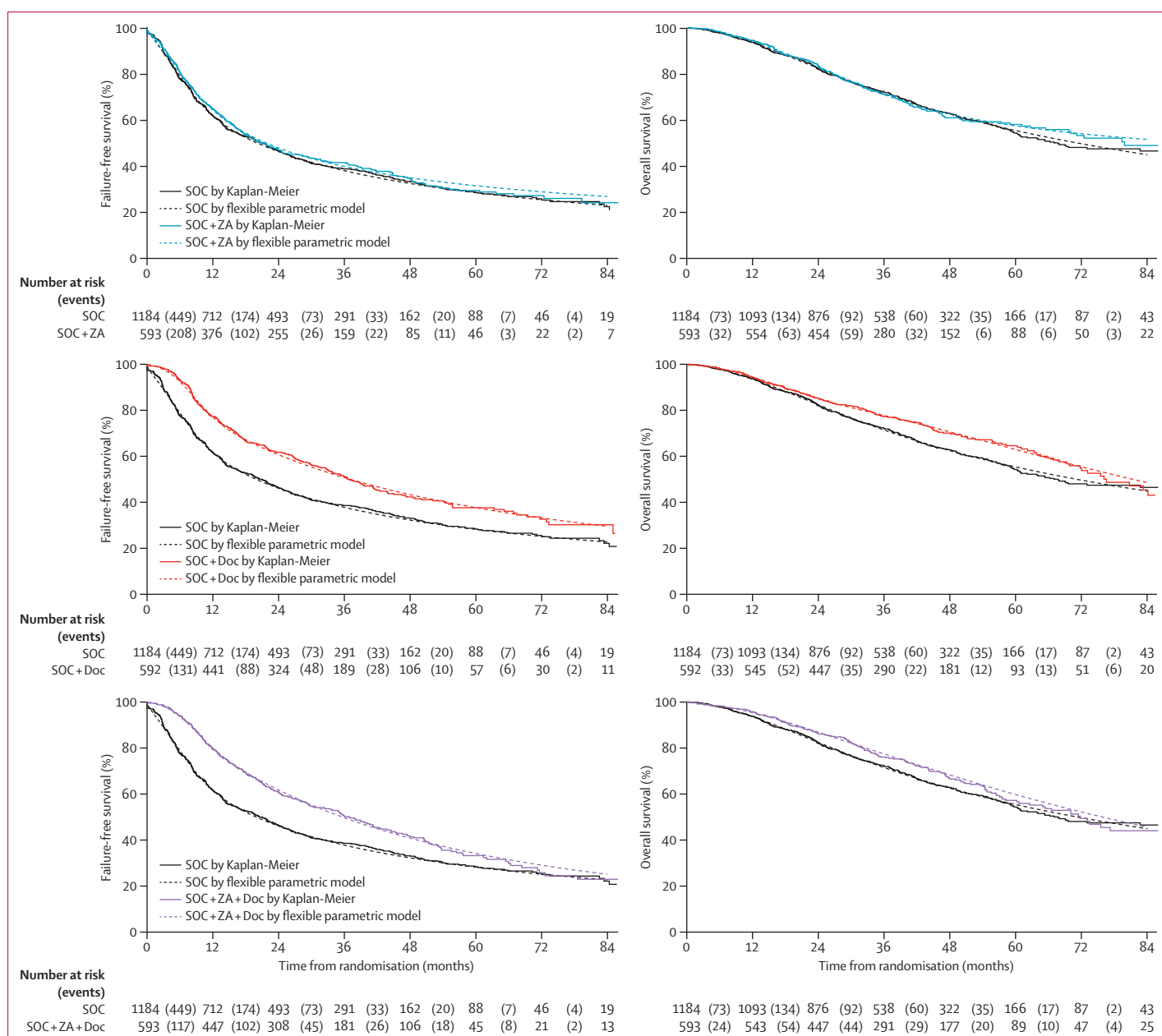


Figure 2: Failure-free and overall survival

Figure shows Kaplan-Meier curves and flexible parametric models fitted to the data. Number at risk (events) shows the number of individuals at risk (ie, the number who were event free) at each timepoint, with parentheses showing the number of individuals who developed events in the period between each timepoint. SOC-only=standard of care only. SOC+ZA=standard of care plus zoledronic acid. SOC+Doc=standard of care plus docetaxel. SOC+ZA+Doc=standard of care plus zoledronic acid and docetaxel.

There was, however, evidence of an improvement in failure-free survival both for SOC+Doc, with 315 events (HR 0.61, 95% CI 0.53–0.70; $p=0.413 \times 10^{-13}$), median failure-free survival 37 months, and 5-year failure-free survival 38%; and for SOC+ZA+Doc, with 318 events (HR 0.62, 95% CI 0.54–0.70; $p=0.134 \times 10^{-12}$), median failure-free survival 36 months, 5-year failure-free survival 34%. There was strong evidence of non-proportional hazards for both comparisons showing an

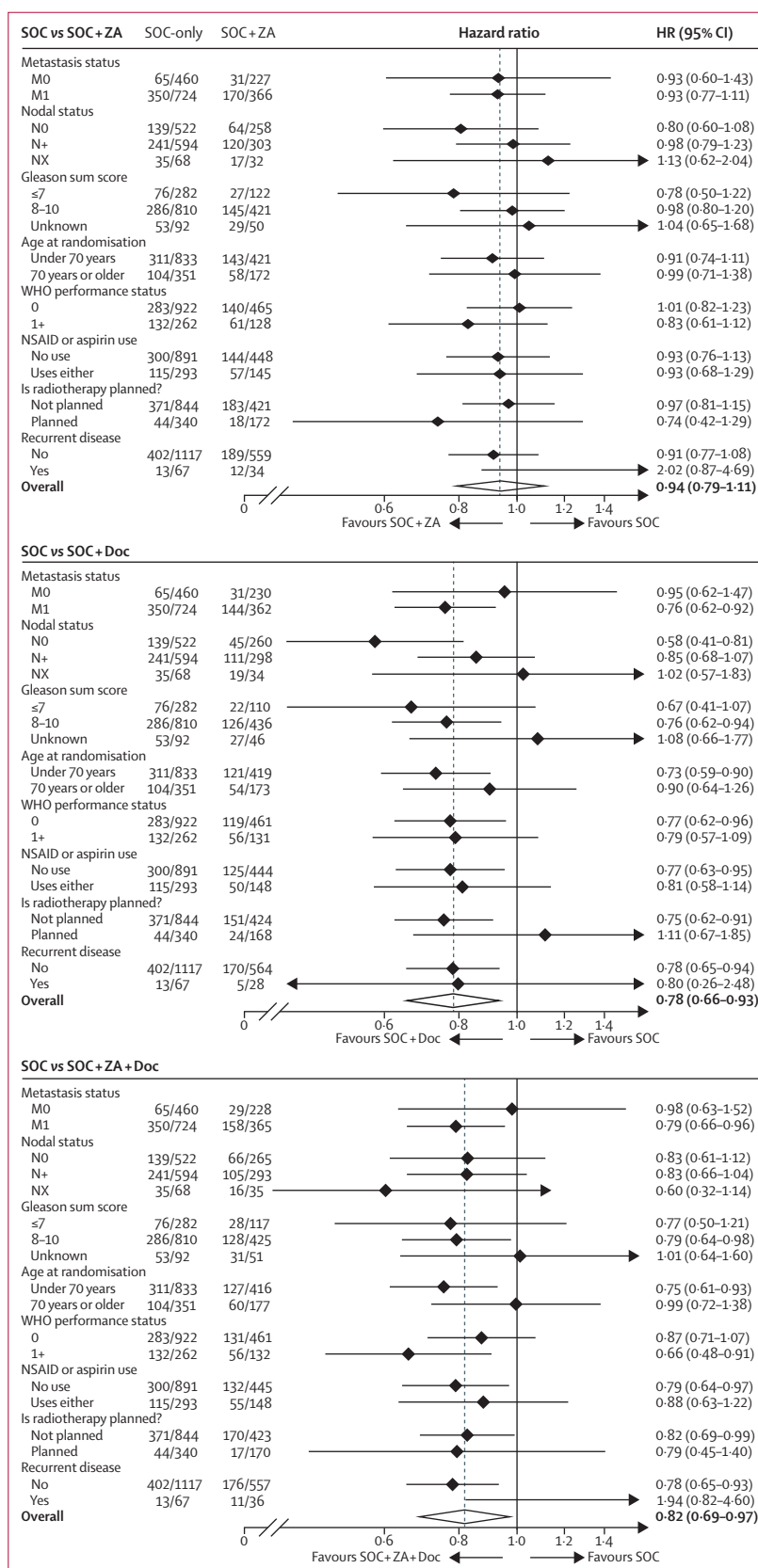
improvement in failure-free survival (SOC+Doc and SOC+ZA+Doc). In these cases, restricted mean survival time is preferred to the hazard ratio for summarising the treatment effect. Mean failure-free survival, restricted to the first 84 months on trial, was 34.8 months on SOC-only, compared to 44.2 months on SOC+Doc (difference 9.4 months, 95% CI 6.6–12.3; $p=0.556 \times 10^{-10}$) and compared to 43.1 months on SOC+ZA+Doc (difference 8.3 months, 95% CI 5.5–11.1; $p=0.480 \times 10^{-8}$).

As with survival, there was no evidence of heterogeneity in failure-free survival across the same predefined subsets (appendix page 3). Considering metastatic status subsets, treatment effect was broadly consistent within both non-metastatic and metastatic populations, for all research comparisons, and indicated that docetaxel improved failure-free survival for non-metastatic disease (HR 0.60, 95% CI 0.45–0.80; $p=0.283 \times 10^{-3}$) as for metastatic disease (HR 0.61, 95% CI 0.53–0.71; $p=0.283 \times 10^{-10}$).

At the time of this analysis, a total of 978 men had died, 809 (83%) from prostate cancer. The proportion of deaths attributed to prostate cancer was increased in men presenting with metastases: 703 (86%) of 822 deaths in the 1817 men presenting with metastases, compared with 106 (68%) of 156 deaths in 1145 men presenting without metastases. Adjusted competing risks regression for prostate-cancer-specific survival showed an advantage over SOC-only for SOC+Doc (subHR 0.79, 95% CI 0.65–0.96; $p=0.019$) and SOC+ZA+Doc (0.78, 0.65–0.95; $p=0.013$), but not SOC+ZA (0.95, 0.79–1.15; $p=0.613$). For patients with metastatic disease, the subHR for SOC+Doc was 0.80 (95% CI 0.65–0.99; $p=0.033$), for SOC+ZA was 0.92 (0.75–1.12), and for SOC+ZA+Doc was 0.78 (0.64–0.96); for patients with non-metastatic disease, the subHR for SOC+Doc was 0.82 (95% CI 0.48–1.40; $p=0.475$), for SOC+ZA was 1.08 (0.66–1.76), and for SOC+ZA+Doc was 0.81 (CI 0.46–1.43). We noted particularly limited power for subset analyses at this time for both settings.

Amongst patients randomly assigned to SOC-only, 328 of 1184 reported at least one skeletal-related event. Time to first skeletal-related event was improved with SOC+Doc (112 patients reported skeletal-related event; HR 0.60, 95% CI 0.48–0.74; $p=0.127 \times 10^{-5}$) and SOC+ZA+Doc (108 patients; HR 0.55, 95% CI 0.44–0.69; $p=0.277 \times 10^{-7}$), but not SOC+ZA (153 patients; HR 0.89, 95% CI 0.73–1.07; $p=0.221$). There was strong evidence of non-proportional hazards for both comparisons showing improvement in time to first skeletal-related event (SOC+Doc and SOC+ZA+Doc). In these cases, restricted mean survival time is preferred for summarising treatment effect. Mean time to skeletal-related event, restricted to within the first 84 months on trial, was 61.4 months (95% CI 59.5–63.2) on SOC-only, compared with 68.0 months on SOC+Doc (difference 6.6 months, 95% CI 3.6–9.6;

Figure 3: Forest plots of treatment effect on survival within subsets
Data are deaths/N or HR (95% CI). All p values were statistically non-significant.
For SOC-only vs SOC+ZA, all $p>0.09$, PSA $p=0.116$, time-period $p=1.000$. For SOC-only vs SOC+Doc, all $p>0.06$, PSA $p=0.589$, time-period $p=1.000$. For SOC-only vs SOC+ZA+Doc, all $p>0.23$ except previously treated $p=0.023$, PSA $p=0.254$, time-period $p=1.000$. X axis provided with natural log scaling. SOC-only=standard of care only. SOC+ZA=standard of care plus zoledronic acid. SOC+Doc=standard of care plus docetaxel. SOC+ZA+Doc=standard of care plus zoledronic acid and docetaxel. PSA=prostate-specific antigen. NSAID=non-steroidal anti-inflammatory drug.



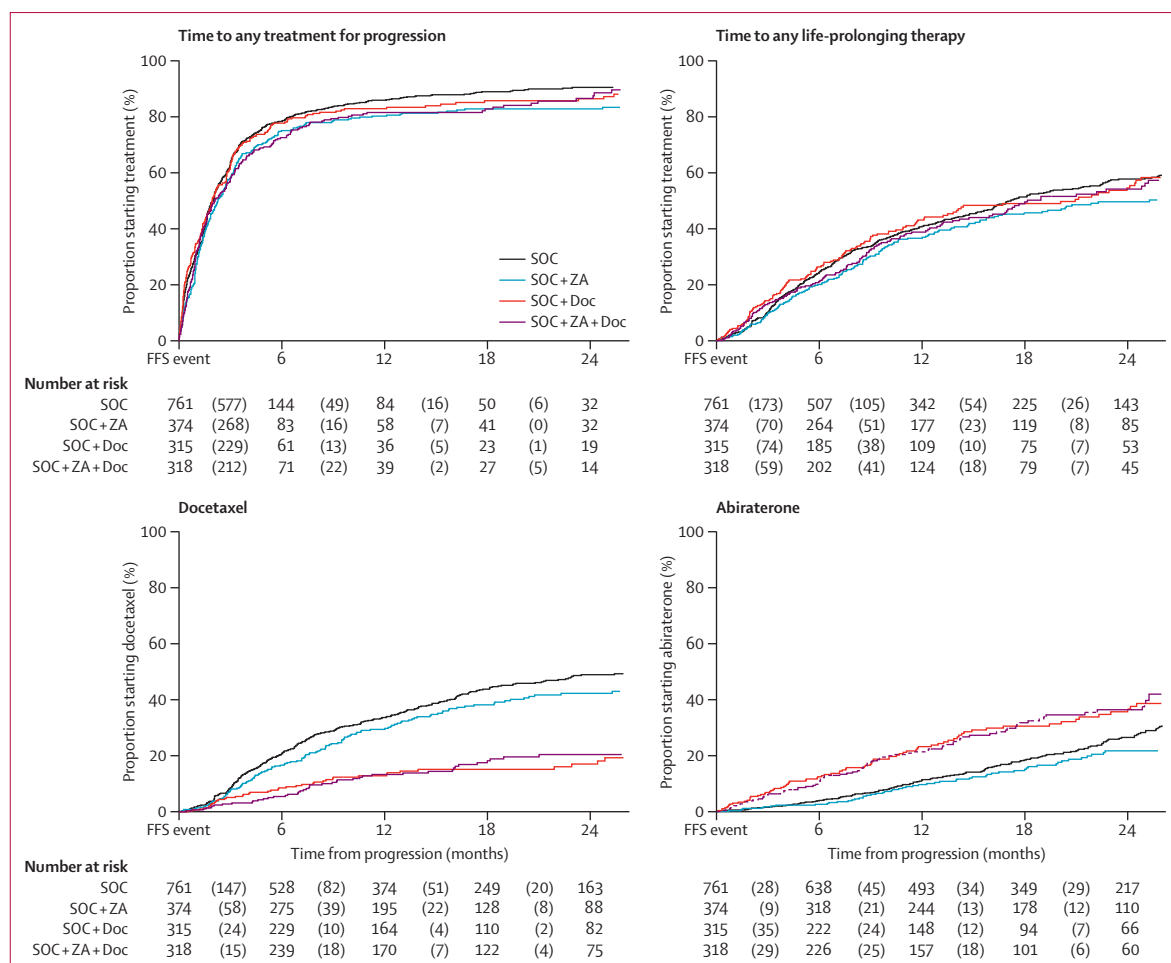


Figure 4: Time to treatment after progression

Figure shows treatments ever used at relapse, at the discretion of the treating clinician, by group, cumulative incidence curves. (A) Time to any treatment after progression. (B) Time to any life-prolonging treatment after progression. (C) Time to docetaxel after progression. (D) Time to abiraterone after progression. SOC-only=standard of care only. SOC + ZA=standard of care plus zoledronic acid. SOC + Doc=standard of care plus docetaxel. SOC + ZA + Doc=standard of care plus zoledronic acid and docetaxel. FFS=failure-free survival.

$p=0.177 \times 10^{-4}$) and 68.3 ($65.6-70.3$) on SOC+ZA+Doc (difference 6.9 months, 95% CI $4.1-9.8$; $p=0.249 \times 10^{-5}$). In the patient group with bone metastases at presentation, SOC+ZA similarly had no evidence of an effect (HR 0.94 , 95% CI $0.76-1.16$; $p=0.564$).

Figure 4 shows time to first of any treatment after a failure-free survival event and time to first life-extending therapy (defined as available agents with proven survival gain in castrate-refractory prostate cancer: docetaxel, abiraterone, cabazitaxel, enzalutamide, and radium-223). There were no obvious differences either in time to any therapy or life-extending therapies between groups. There were however, differences in the pattern of therapy depending on whether patients were docetaxel-exposed upfront (figure 4). Analysis of zoledronic acid use after relapse is provided in the appendix page 7. Overall exposure to treatment for progression is summarised in table 4, showing slightly higher rates of exposure to subsequent therapy in the control group. Use of

cabazitaxel, enzalutamide, and radium-223 were low across all groups (appendix page 6).

The proportion of patients reporting worst adverse event ever as grade 3 or higher was highest with SOC+Doc (288 patients [52%]) and SOC+ZA+Doc (269 [52%]; table 5). This was mostly due to events during the first 6 months on trial, when the proportions were 17% ($n=203$) for SOC-only, 15% ($n=91$) for SOC+ZA, 36% ($n=198$) for SOC+Doc, and 39% ($n=202$) for SOC+ZA+Doc, with docetaxel seeming to contribute the most toxicity. For 1998 patients with adverse event data around 1 year after randomisation (ie, worst adverse event grade reported at 48 or 60 weeks of follow-up), the proportions of grade 3 or higher toxic effects were balanced, with 10% ($n=76$) patients reporting a worst adverse event as grade 3 or higher with SOC-only, 10% ($n=41$) with SOC+ZA, 10% with ($n=43$) SOC+Doc, and 12% ($n=49$) with SOC+ZA+Doc. The pattern and levels of adverse events were similar in the safety and intention-to-treat populations. There were ten

(2%) reported cases of osteonecrosis of the jaw on SOC+ZA and 20 (4%) on SOC+ZA+Doc. There were eight deaths probably or possibly related to the research treatment: one on SOC+Doc (neutropenic sepsis), and seven on SOC+ZA+Doc (four neutropenic sepsis, one pneumocystic pneumonia, one interstitial pneumonitis, and one pneumonia).

Discussion

The STAMPEDE randomised controlled trial is investigating the effectiveness of the front-line use of various treatments in men commencing long-term hormone therapy for newly diagnosed locally advanced or metastatic prostate cancer, or who have relapsed after local therapy with poor prognosis features. The MAMS design used in STAMPEDE has allowed us to address multiple treatment questions simultaneously within a single trial platform.¹⁸ We will report further randomised comparisons from STAMPEDE in the coming years (appendix page 2), meaning that, through this single protocol, we will have answered at least eight different primary questions in 15 years. To have addressed as many questions in separate, sequential trials would have taken many decades and far more patients, notably allocated to control groups. We recommend that academic and industry researchers consider this design in the future, to make faster progress and good use of limited trial resources.

These are the first mature, comparative, randomised data to emerge from the trial. We found that the addition of docetaxel to standard of care was associated with improved survival, with an HR of 0.78 and a difference in median survival of 10 months, as well as improvements in prostate-cancer-specific survival, failure-free survival, and skeletal-related events. The combination of zoledronic acid and docetaxel was associated with similar improvements, although the benefit observed was smaller. We will report cost-effectiveness and patient-reported outcomes separately.

Docetaxel is a widely used drug with a familiar toxicity profile. Docetaxel was well tolerated in this population, with most patients completing all six cycles in a timely fashion and good dose intensity. Predictable chemotherapy toxic effects, including neutropenia and febrile neutropenia, were observed but few patients stopped treatment because of side-effects. Toxic effects in both docetaxel-containing groups seemed higher than in previous studies of this drug in patients with castrate-refractory prostate cancer (eg, TAX327), but the studies have used different populations.^{27,28} The protocol made no recommendations about growth factor support, and we have not collected information about its use.^{29,30}

Docetaxel significantly prolonged failure-free and overall survival across the trial population with no evidence that the effect varied across different groups in the population; in particular, there is no evidence of a difference of the effect of docetaxel by metastatic status,

	Standard of care	Standard of care plus zoledronic acid	Standard of care plus docetaxel	Standard of care plus zoledronic acid and docetaxel
Patients with progression	761	374	315	318
Reported new treatment	671 (88%)	303 (81%)	260 (83%)	257 (81%)
Reported (new) life-extending treatment	383 (50%)	172 (46%)	139 (44%)	136 (43%)
Life-extending treatment				
Docetaxel	313 (41%)	136 (36%)	44 (14%)	49 (15%)
Abiraterone	177 (23%)	72 (19%)	89 (28%)	88 (28%)
Enzalutamide	66 (9%)	18 (5%)	25 (8%)	26 (8%)
Cabazitaxel	26 (3%)	14 (4%)	22 (7%)	30 (9%)
Radium-223	6 (1%)	1 (0%)	6 (2%)	3 (1%)
Other treatments				
Anti-androgens	512 (67%)	234 (63%)	181 (57%)	174 (55%)
Zoledronic acid	128 (17%)	50 (13%)	35 (11%)	36 (11%)
Dexamethasone	104 (14%)	42 (11%)	39 (12%)	29 (9%)
Diethylstilbestrol (also known as stilboestrol)	84 (11%)	43 (11%)	38 (12%)	41 (13%)
Prednisolone	72 (9%)	22 (6%)	28 (9%)	23 (7%)
Other chemotherapy*	26 (3%)	17 (5%)	21 (7%)	15 (5%)
Other bisphosphonate†	22 (3%)	3 (1%)	8 (3%)	5 (2%)
Strontium	12 (2%)	3 (1%)	2 (1%)	4 (1%)
Cox-2 inhibition	0 (0%)	1 (0%)	0 (0%)	0 (0%)

*Not docetaxel or cabazitaxel. †Not zoledronic acid

Table 4: Treatments ever used at relapse, at the discretion of the treating clinician

for either of these outcome measures. The beneficial effect on survival is clear in the larger metastatic subpopulation, which accounted for 61% of patients in the trial and 84% of deaths. There were fewer patients with non-metastatic disease and, with their generally more favourable prognosis, there were relatively few deaths in this group; all survival analyses for this subset are currently underpowered. In this non-metastatic subset of men, death from causes other than prostate cancer was more common than in men with metastatic disease, and therefore any effect of docetaxel on overall survival will be diluted. We will report longer-term follow-up in due course, but note that estimates of the treatment effect in failure-free survival and prostate-cancer-specific survival are extremely similar for patients with and without metastases at presentation.

For zoledronic acid, the results show no evidence of efficacy on failure-free survival, skeletal-related events, or overall survival, despite good compliance with therapy and good levels of exposure, with target duration of 2 years. Few patients stopped treatment for side-effects; the most frequent reason for stopping trial therapy within 2 years was disease progression. This differed between the SOC+ZA and SOC+ZA+Doc groups because failure-free survival was increased in the latter group by docetaxel, indirectly leading to increased exposure to zoledronic acid as well. Despite this increased exposure, zoledronic acid showed no

	Standard of care (n=1184)	Standard of care plus zoledronic acid (n=593)	Standard of care plus docetaxel (n=592)	Standard of care plus zoledronic acid and docetaxel (n=593)
Safety population				
Number of patients included in analysis*	1228	608	550	516
Grade 1–5 adverse event	1213 (99%)	604 (99%)	550 (100%)	515 (100%)
Grade 3–5 adverse event	399 (32%)	197 (32%)	288 (52%)	269 (52%)
Grade 5 adverse event	5	1	4	6
Most frequent adverse events reported as grade 3–5				
Endocrine disorder (including impotence, hot flushes)	145 (12%)	74 (12%)	57 (10%)	64 (12%)
Febrile neutropenia	15 (1%)	5 (<1%)	84 (15%)	74 (14%)
Neutropenia (neutrophils)	6 (0%)	3 (<1%)	66 (12%)	62 (12%)
General disorder (including lethargy, fever, asthenia)	46 (4%)	28 (5%)	34 (7%)	56 (11%)
Musculoskeletal (including bone pain, generalised pain)	69 (6%)	35 (6%)	32 (6%)	44 (9%)
Gastrointestinal disorder (including diarrhoea, abdominal pain, constipation, vomiting)	36 (3%)	19 (3%)	45 (8%)	37 (7%)
Renal (including renal impairment, urinary-tract infection)	71 (6%)	30 (5%)	23 (4%)	25 (5%)
Notable adverse events				
Respiratory disorder (including dyspnoea, upper respiratory-tract infection)	27 (2%)	13 (2%)	29 (5%)	23 (4%)
Cardiac disorder (including hypertension, myocardial infarction)	35 (3%)	19 (3%)	16 (3%)	19 (4%)
Osteonecrosis of the jaw	0 (0%)	10 (2%)	0 (0%)	21 (4%)
Nervous system other (including peripheral neuropathy)	20 (2%)	8 (1%)	19 (3%)	19 (4%)
Nail changes	0 (0%)	0 (0%)	5 (1%)	4 (1%)
ITT population				
Number of patients included in analysis†	1173	587	579	563
Grade 1–5 adverse event	1160 (99%)	583 (99%)	577 (100%)	562 (100%)
Grade 3–5 adverse event	375 (32%)	184 (31%)	298 (51%)	296 (53%)
Grade 5 adverse event	4	1	4	7
Grade 5 adverse events were not necessarily treatment-related; similarly treatment-related deaths were not always grade 5 adverse events. ITT=intention-to-treat. *Analysis by actual treatment initiated (irrespective of assigned study arm) in patients who underwent adverse event assessment. †Analysis by assigned study arm in patients who underwent adverse event assessment.				
Table 5: Worst adverse event (grade) reported over entire time on trial				

evidence of an advantage when added to docetaxel (HR 1.06).

The effect of docetaxel on survival was positive, but clinically significant toxicity did occur; in clinical practice, consideration could be given to early use of growth factor support to enable treatment delivery. There was one treatment-related death in the SOC+Doc group and seven in the combination group. This difference, combined with a more modest survival benefit for the combination treatment, raises the possibility of some interaction (or antagonism) between docetaxel and zoledronic acid in the treatment of this group of men.

A number of trials have now examined docetaxel in the hormone-naïve context in both the non-metastatic and metastatic settings, of which STAMPEDE is the largest.^{25,26,31–34} These findings are discussed elsewhere but consistently show an improvement in failure-free survival.¹⁴ The CHAARTED trial²⁵ recently reported improved survival in metastatic disease whereas GETUG-15,²⁶ a similar trial, did not report a differential effect. Taken with our results, there is compelling evidence

that front-line docetaxel substantially improves survival in patients with metastatic disease. In the non-metastatic setting, there are insufficient mature survival results in the literature, so further follow-up and engagement in planned meta-analyses are needed to further delineate the effect of docetaxel on survival in this setting. The impact on failure-free survival is both clear and large in favour of docetaxel in STAMPEDE.

The case mix of patients joining the trial included men with newly diagnosed disease and a small proportion of patients with recurrent disease. The recurrent disease subset is small and thus it is unrealistic to look for statistically reliable results in such men; however, we note that estimates of the effect of docetaxel are consistent with that seen in the population as a whole.

For zoledronic acid, there are now several trials showing no evidence of a survival gain with upfront use,^{14,35–37} as discussed in the accompanying meta-analysis. This contrasts with the results from MRC PR05¹⁵ with sodium clodronate (another bisphosphonate), in which a survival benefit was reported in a metastatic population. The

companion non-metastatic trial showed no evidence of an effect on survival with the same agent.¹⁵

Men in the STAMPEDE trial did better than we had expected in terms of survival. We believe this resulted from second-line and third-line treatments which were unavailable when the trial was designed. The timing of second-line therapy after relapse was similar across groups, but choice of which treatment to use was at the investigator's discretion, and, consequently, was varied. This choice would have been affected by local practice and availability of newer treatments over time, such as abiraterone, enzalutamide, radium-223, and cabazitaxel, as well as allocated treatment in the trial.

There are several strengths to note in the STAMPEDE trial and specifically for the analyses reported here. First, the data were prospectively collected and randomised, from nearly 3000 men with patient characteristics that were well balanced by group, and we achieved good median follow-up (43 months). Second, the data were very recently frozen (May, 2015) at a pre-planned analysis point of roughly 400 control group deaths, meaning the primary outcome results are both well powered and have been reported promptly. Third, the patients contributing to these analyses came from more than 100 sites across the UK and Switzerland, suggesting the results to be generalisable. Fourth, the design allows easy understanding of effect across multiple randomisations. Finally, treatment compliance among patients starting treatment was good.

We are aware that there are also limitations within the data. First, the proportion of patients not starting treatment, especially docetaxel, will have a small diluting effect. Linkage to hospital records is required to report more detailed information on skeletal-related events. The impact of therapies that do not target androgen receptors on recurrence (as assessed by prostate-specific antigen) is likely to be complex. Finally, power for assessing the consistency of effects across subsets is inevitably low; we will report long-term follow-up in due course when the maturity will be much greater both across the trial and particularly in the non-metastatic subset.

In conclusion, we have shown improved survival across a population of men commencing first-line long-term hormone therapy through the addition of docetaxel chemotherapy but not by adding zoledronic acid. Therefore, zoledronic acid should not become part of standard of care. Standard of care should be updated to include docetaxel chemotherapy in suitable patients with metastatic disease, and docetaxel may be considered for men with high-risk non-metastatic prostate cancer with or without radiotherapy.

Contributors

NDJ designed these trial comparisons, was a grant holder, collected or collated data, interpreted data, wrote critical sections of the report, and reviewed and agreed the manuscript. MRSy designed these trial comparisons, was a grant holder, collected or collated data, performed or oversaw statistical analyses, interpreted data, wrote critical sections of the report, and reviewed and agreed the report. NWC, MDM, and DPD

designed these trial comparisons, were grant holders, collected or collated data, interpreted data, and reviewed and agreed the report. MRSp collected or collated data, performed or oversaw statistical analyses, interpreted data, wrote critical sections of the report, and reviewed and agreed the report. AWSR collected or collated data, interpreted data, wrote critical sections of the report, and reviewed and agreed the report. CCP, JMR, GA, JdB, WC, RJJ, GT, CA, DM, RM, MA, SBe, AJB, SBr, RC, PC, SC, AC, TE, JG, SG, JDG, JH, RH, RL, FM, DBM, JMOS, OP, CCP, AP, AJR, NS, RS, JS, SS, ST, DT, and JW collected or collated data, interpreted data, and reviewed and agreed the report. MKBP conceived the original MAMS idea, designed these trial comparisons, was a grant holder, collected or collated data, performed or oversaw statistical analyses, interpreted data, wrote critical sections of the report, and reviewed and agreed the report.

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Declaration of interests

GA reports personal fees from Sanofi-Aventis; personal fees and non-financial support from Astellas; personal fees from Novartis; grants, personal fees, and non-financial support from Janssen, personal fees and non-financial support from Roche/Ventana, personal fees and non-financial support from Medivation, personal fees from Millennium Pharmaceuticals, personal fees and non-financial support from Abbott Laboratories, personal fees from Essa Pharmaceuticals, personal fees and non-financial support from Bayer Healthcare Pharmaceuticals, personal fees from Takeda, and grants from AstraZeneca. AJB reports other support from Janssen, Sanofi, and Astellas, outside the submitted work. RC reports personal fees as a Consultant for Sanofi-Aventis, outside the submitted work. SC reports grants and personal fees from Sanofi-Aventis, outside the submitted work. JdB reports advisory boards and paid participation for Sanofi-Aventis. DPD reports grants from Cancer Research UK, during the conduct of the study; personal fees from Takeda Pharmaceuticals, outside the submitted work. TE reports that patients entering this study received docetaxel free of charge (Sanofi) and has previously received per-patient payment for entering patients in other commercial trials investigating docetaxel. JDG reports other support as a local principal investigator for a study of radium-223 in prostate cancer funded by Bayer, and other support as a local principal investigator for a study of LHRH antagonist in prostate cancer funded by Millennium Pharmaceuticals, outside the submitted work. NDJ reports grants and personal fees from Sanofi, and grants and personal fees from Novartis, during the conduct of the study; grants and personal fees from Janssen, grants and personal fees from Astellas, and grants and personal fees from Bayer, outside the submitted work. RJJ reports grants from Sanofi, and grants and non-financial support from Novartis, during the conduct of the study; grants, personal fees, and non-financial support from Sanofi, grants, personal fees, and non-financial support from Novartis, outside the submitted work. MDM reports personal fees from Sanofi, personal fees from Bayer, personal fees from Dendreon, personal fees from Bristol-Myers, and personal fees from Janssen, outside the submitted work. CCP reports personal fees from Sanofi-Aventis, research funding and speaker's honoraria from Bayer, and Bavarian Nordic and Janssen, outside the submitted work. MKBP reports funding from Cancer Research UK, Medical Research Council, Novartis, Sanofi-Aventis, Pfizer, Janssen, Astellas, NIHR Clinical Research Network (formerly

National Cancer Research Network), and SAKK—Swiss Group for Clinical Cancer Research, during the conduct of the study. JMR reports personal fees from Janssen (lecture fee), outside the submitted work. MRSp reports grants and non-financial support from Sanofi-Aventis, grants and non-financial support from Novartis, grants and non-financial support from Pfizer, grants and non-financial support from Janssen, and grants and non-financial support from Astellas, during the conduct of the study. JS reports support for travel and speakers fees for the following companies in the field of prostate cancer, not related to this paper: Janssen Bayer and Astellas. SS reports personal fees and non-financial support from Sanofi-Aventis, outside the submitted work. MRSy reports grants and non-financial support from Sanofi-Aventis, grants and non-financial support from Novartis, grants and non-financial support from Pfizer, grants and non-financial support from Janssen, grants and non-financial support from Astellas, during the conduct of the study; and personal fees from Eli-Lilly, outside the submitted work. ST reports other from Sanofi, other support from Astellas, personal fees from Astellas, and other support from Janssen, outside the submitted work. JW reports a paid consultancy for Janssen. Abiraterone acetate was developed at The Institute of Cancer Research, which therefore has a commercial interest in the development of this agent. All other authors declare no competing interests.

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